IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Date: February 3, 2005

Parent Application

In re application of : Sunigawa et al.
International Application No.: PCT/JP2002/07963
Publication Number: WO 2004/012814
International Filing Date: August 5, 2002
Priority Date Claimed: August 5, 2002
For: MEDICAL TREATMENT SYSTEM BY SUBSTITUTING NATIVE BIOLOGICAL REGULATORY FUNCTION; CARDIAC PACING SYSTEM, BLOOD PRESSURE REGULATING SYSTEM, AND CARDIAC DISEASE TREATMENT SYSTEM BASED ON THE MEDICAL TREATMENT SYSTEM
Attorney Docket No.: KUP-5

TRANSLATION OF SPECIFICATION AS FILED

DT05 Rec'd PCT/PTO 03 FEB 2005

SPECIFICATION

Medical Treatment System by Substituting Native Biological Regulatory Function; Cardiac Pacing System, Blood Pressure Regulating System, and Cardiac Disease Treatment System based on the Medical Treatment System

Technical Field

The present invention is related to a system to treat diseases by substituting native biological regulatory function; a cardiac pacing system, a blood pressure regulating system and a cardiac disease treatment system, all of which are based on the above medical treatment system. The object of the present invention is to provide a system to treat diseases by substituting native biological regulatory function, that is capable of regulating organs as if their central controllers were normally functioning even if the central controllers themselves become abnormal by various causes; a cardiac pacing system, a blood pressure regulating system, and a cardiac disease treatment system, all of which are based on the above medical treatment system.

Background Technology

Heart transplantation from subjects falling into brain death became legal in Japan, to be a new treatment method for patients with severe heart failure. However, the number of heart donors is definitely small, and the shortage of hearts for transplantation has been seriously discussed not only in Japan but also worldwide.

An alternative treatment for the patients with severe cardiac failure is artificial heart implantation. However, even the most recent artificial hearts are not regulated by native biological regulation, thereby are not always operating in concert with native organs.

Pacemakers have been used for the treatment of patients with bradycardia. Pacemakers enable necessary rhythmic myocardial contraction by electrically stimulating myocardium artificially.

Recently rate-responsive pacemakers have been developed, in which stimulation rate changes according to the estimated native heart rate from e.g., electrocardiographic QT time, body temperature, or body acceleration. However, specificity, sensitivity and transient response of heart rate regulation compared to native heart rate regulation by such pacemakers have not been always satisfactory.

In some other diseases, it is well known that abnormal native regulatory function rather promotes disease processes. For example, it is known that abnormal native regulatory mechanisms participate in the progression of the heart disease, and it is well known that sympathetic nerve overactivation and abnormal vagal nerve withdrawal occur after the onset of acute myocardial infarction, only to worsen the outcome.

Such abnormal native regulatory function can also be observed in circulatory diseases other than heart diseases.

Even in normal subjects, 300 to 800 mL of blood is shifted to be stored in the lower extremity and internal organs below the heart level during standing, causing decreased venous return to the heart and hypotension. Normal subjects are usually provided with a blood pressure regulating mechanism to antagonize this and to maintain blood pressure constant, and thereby orthostatic hypotension is prevented. Subjects with various disorders with damaged blood pressure regulating system, however, suffer from orthostatic hypotension. For example, in patients with Shy-Drager syndrome, a part of nervous system involved in blood pressure regulation becomes abnormal, and the quality of life is seriously impaired due to large fluctuations in blood pressure with their body position change.

Artificial organs and artificial devices, such as conventional artificial hearts and cardiac pacemakers, are not always operating in concert with native organs, as described above, because they are not intended to be controlled by native regulatory system. Therefore their performance, in terms of sensitivity to changes in native organs, was not satisfactory.

Pharmacological treatment with drugs such as coronary vasodilators, β-adrenergic blockers and anti-platelet agents, catheter-based interventional treatment, and coronary artery bypass surgery have been developed as the treatment for myocardial infarction.

However, even by taking full advantage of all pharmacological, interventional and surgical treatments, progression of pathology even to death might often be inevitable.

Adrenergic agonists, such as epinephrine, levodopa and amphetamine, are used for the pharmacological treatment of the Shy-Drager syndrome with severe orthostatic hypertension, and of excessive salt is administered for the symptomatic relief. Although symptoms can be alleviated to some extent, it is impossible to treat the Shy-Drager syndrome to full functional restoration.

The object of the present invention is to provide a system to treat diseases, that is capable of regulating organs as if their central controllers were normally functioning even if the central controllers themselves become abnormal by various causes; a cardiac pacing system, a blood pressure regulating system, and a cardiac disease treatment system, all of which are based on the above medical treatment system.

Disclosure of the Invention

The invention described in Claim 1 is related to a system to treat diseases based on biological activities, comprising: biological activity sensing means which senses biological activity information issued by biological activities, and outputs biosignals; calculating means which receives the biosignals sensed by the biological activity sensing means, analyzes and processes the biosignals to calculate signals for the stimulation of organisms, and outputs the signals for the stimulation of organisms; and organism stimulating means which receives the signals for the stimulation of organisms calculated by the calculating means, and stimulates the organism on the basis of the signals for the stimulation of organisms.

The invention described in Claim 2 is related to a system to treat disease based on biological activities, comprising: biological activity sensing means which senses biological activity information issued by biological activities, and outputs biosignals; calculating means which receives the biosignals sensed by the biological activity sensing means, analyzes and processes the biosignals to calculate signals for the stimulation of organisms, and outputs the signals for the stimulation of organisms; and organism stimulating means which receives the signals for the stimulation of organisms calculated by the calculating means, and stimulates the organism on the basis of the signals for the stimulation of organisms, wherein the calculating means includes discriminating means which discriminates whether the received biosignals are caused by normal biological activities or by abnormal biological activities, the calculating means does not output the signals for the stimulation of organisms when the received biosignals are discriminated to be caused by normal biological activities, and the calculating means outputs the signals for the stimulation of organisms when the received biosignals are discriminated to be caused by abnormal biological activities.

The invention described in Claim 3 is related to a system to treat diseases based on biological activities according to Claim 1 or 2, wherein signals for the stimulation of organisms are calculated by

convolution integral between impulse response previously obtained from normal biological activities and the biosignals sensed by the biological activity sensing means.

The invention described in Claim 4 is related to a cardiac pacing system based on biological activities, comprising: nerve activity sensing means which senses nerve activities of cardiac sympathetic nerve and/or vagal nerve, and outputs nerve activity signals; calculating means which receives the nerve activity signals sensed by the nerve activity sensing means, analyzes and processes the nerve activity signals to calculate pacing signals for the control of heart rate, and outputs the pacing signals; and pacing means which receives the pacing signals calculated by the calculating means, and stimulates the heart on the basis of the pacing signals to regulate heart rate.

The invention described in Claim 5 is related to a blood pressure regulating system, which uses the native regulation rule to estimate nerve activities in response to blood pressure changes, comprising: blood pressure sensing means which senses blood pressure and outputs a blood pressure signal; calculating means which receives the blood pressure signal sensed by the blood pressure sensing means, analyzes and processes the blood pressure signal to calculate sympathetic nerve stimulation signal for the regulation of blood pressure by the stimulation of sympathetic nerve innervating vascular beds, and outputs the sympathetic nerve stimulation signal; and nerve stimulating means which receives the sympathetic nerve stimulation signal calculated by the calculating means, and stimulates the sympathetic nerve innervating vascular beds on the basis of the sympathetic nerve stimulation signal for the regulation of blood pressure.

The invention described in Claim 6 is related to a system to treat cardiac diseases based on biological activities, comprising: cardiovascular activity sensing means which senses cardiovascular activity information issued by cardiovascular system, and outputs cardiovascular activity signals; calculating means which receives the cardiovascular activity signals sensed by the cardiovascular activity sensing means, analyzes and processes the cardiovascular activity signals to calculate nerve stimulation signals, and outputs the nerve simulation signals; and nerve stimulating means which receives the nerve stimulation signals calculated by the calculating means, and stimulates the nerve on the basis of the nerve stimulation signals.

Brief Description of the Drawings

Figure 1(a) is a schematic illustration showing the components consisting of native normally functioning baroreflex, and Figure 1(b) is a schematic illustration showing how to apply the system for treating diseases based on this invention to native abnormally functioning baroreflex.

Figure 2 is a block diagram depicting the outline of the system for treating diseases based on this invention.

Figure 3 is a graph showing the relationship between sympathetic nerve activity and heart rate of a representative rabbit. Figure 3(a) shows the changes in sympathetic nerve activity and heart rate with time, Figure 3(b) is a scatter plot showing the relationship between sympathetic nerve activity and simultaneous heart rate, obtained by data shown in Figure 3(a). Figure 3(c) is a scatter plot between the predicted heart rate obtained from sympathetic nerve activity and impulse response, i.e., the required heart rate by organisms, on one hand, and the measured heart rate on the other.

Figure 4 is a graph showing results obtained in Test Example 1.

Figure 5 is a graph showing results obtained in Test Example 2.

Figure 6 is a graph showing results obtained in Test Example 3.

Figure 7 is a graph showing results obtained in Test Example 4.

Figure 8 is a graph showing results obtained in Test Example 6, wherein Figure 8(a) shows orthostatic blood pressure changes of rats with impaired blood pressure regulation but treated with stellate ganglion stimulation, Figure 8 (b) shows orthostatic blood pressure changes of normal rats, and Figure 8(c) shows orthostatic blood pressure changes of rats with impaired blood pressure regulation.

The Preferred Embodiment for Implementation of the Invention

The system to treat diseases disclosed by this invention is capable of restoring native regulatory function as if the lost or abnormal native regulatory functions became normally functioning by substituting the lost or abnormal native functions with the system. We explain the system by describing the application of the invention to blood pressure regulation in details. Figure 1(a) is a schematic illustration showing the components consisting of native baroreflex or blood pressure regulation system. Information about the changes in blood pressure is transmitted from baroreceptors to solitary tract nucleus in medulla oblongata. The solitary tract nucleus then in turn changes sympathetic nerve activity to regulate blood pressure by e.g., vasoconstriction. Figure 1(b) is a schematic illustration where we applied the system to treat diseases (1) based on this invention, which enables to maintain normal blood pressure regulation even with the native vasomotor center fails to achieve normal function by various causes. This is to say that blood pressure can be maintained in a normal way by sensing blood pressure with blood pressure sensing means (2), by converting the blood pressure signal into the signal for the stimulation of nerves with nerve stimulating means (4) by calculating means (3), and by stimulating the nerve with nerve stimulating means (4) according to the calculated signals.

In the following paragraphs we describe the system to treat diseases disclosed in this invention in more details with reference to the figures. Figure 2 is a block diagram depicting the outline of the system to treat diseases based on this invention. The system to treat diseases (1) disclosed in this invention consists of, at least, biological activity sensing means (2), calculating means (3), and organism stimulating means (4).

The biological activity sensing means (2) can output biosignals to the following calculating means (3) by sensing biological activity information issued by biological activities of organisms (S). Examples of the biological activity sensing means (2) include electrodes and pressure sensors.

Biosignals sensed by the biological activity sensing means (2) include, for example, but not limited to sympathetic nerve activities and parasympathetic nerve activities, blood flow, blood pressure, body temperature, electrocardiogram, electroenchephalogram, and various biochemical markers. One can choose any necessary biosignals that are required for the system to achieve the purpose.

Numbers of the biological activity sensing means (2) of the system to treat diseases (1) in this invention are not limited. Although we have shown only one biological activity sensing means (2) for the system to treat diseases (1) in Figure 2, two or more biological activity sensing means may be supplied to meet the requirements of the system to treat diseases in this invention. These two or more biological activity sensing means may be located at the same site or at different sites within the organisms.

The calculating means (3) can analyze and process biosignals sensed by the biological activity sensing means (2) and transferred to the calculated means, to calculate the signals to stimulate organism. The calculated signals to stimulate organism are transferred to the following organism stimulation means (4).

More specifically, the biosignals sensed by the biological activity sensing means (2) are fed into amplifiers (31) in the calculating means (3) for signal amplification. These amplifiers (31) preferably

include filters (not shown) capable of eliminating unnecessary higher or lower frequency biosignals or power line noises.

The amplified signals are converted from analog to digital signals with the aid of analog-to-digital (A/D) converters (32), and then transferred to analyzers/processors (33).

The analyzers/processors (33) process data to calculate signals to be transferred to organism stimulating means (4).

We explain how the calculating means (3) analyzes and processes biosignals, using an example for the regulation of heart rate. Figure 3(a) is a graph showing simultaneously measured changes in cardiac sympathetic nerve activity and heart rate with time. Although, as shown in Figure 3(a), there is a tendency that heart rate increases with increase in cardiac sympathetic nerve activity, correlation between nerve activity and simultaneous heart rate is poor (see Figure 3(b)). Therefore, it is impossible to regulate heart rate using sympathetic nerve activity itself.

With an impulse response function of heart rate in response to sympathetic nerve activity, however, it is possible to estimate heart rate, which is considered to follow requirements of organisms. Figure 3(c) is a scatter plot between heart rate estimated from impulse response function and measured sympathetic nerve activity on one hand, and measured heart rate on the other. As shown in this figure, measured and estimated heart rate correlated well (correlation function 0.93).

Therefore, by analyzing and processing nerve activity signals by calculating means (3), heart rate actually required by organisms can be obtained. In the above example, one can regulate heart rate by stimulating heart electrically according to the estimated heart rate, as if it were regulated by normal central nervous system.

In addition to the above-described example for heart rate regulation, similar related explanations are possible for other various native regulations that are essential for the maintenance of biological functions, such as blood pressure regulation.

Discriminating means (not shown), judging whether biosignals coming into the calculating means (3) arises from normal biological activities or from abnormal biological activities, may also be provided in the calculating means (3). For the discrimination of input biosignals between those from normal and abnormal biological activities, information about normal-activity biosignals are stored in memory means (not shown), and the input biosignals are compared with the stored information. When the difference exceeds a previously determined threshold for a given time period, the signals are judged to be abnormal-activity signals.

When the discriminating means is provided, the calculating means does not output signals to the organism stimulating means for input of normal-activity biosignals, and the native regulatory system itself works. On the other hand, for abnormal-activity biosignals, the system works so that the signals to stimulate organisms are prepared for the organism stimulating means by analyzing and processing biosignals to correct the abnormal biological activity. In other words, for inputs of normal biological activities, the system needs no action to be performed to maintain normal activities. For inputs of abnormal biological activities, the system outputs signals to correct abnormal biological activities to normal biological activities.

When more than one biological activity sensing means are provided, the analysis and processing described above are performed for each respective biological activity sensing means.

The organism stimulating means (4) receives the signals to stimulate organisms from the calculating means (3), and stimulates the organism based on the signals to stimulate organisms. Examples of stimulation by the organism stimulating means (4) may include electrical stimulation of nerves,

myocardium, cerebrum and cerebellum, stimulation with the use of devices for drug administration, artificial pancreas, artificial hearts, and artificial ventilators.

In the following section, we explain the system to treat diseases described in the present invention in detail with reference to more specific examples. First, we explain the cardiac pacing system, the system to treat diseases described as the first embodiment of the present invention.

The basic structure of the cardiac pacing system according to the first embodiment is the same as the system (1) shown in Figure 2. The cardiac pacing system according to the first embodiment comprises at least the biological activity (in this case, nerve activity) sensing means (2), the calculating means (3) and the organism stimulating (in this case, cardiac pacing) means (4).

The biological activity (nerve activity) sensing means (2) senses the nerve activity of the cardiac sympathetic nerve and/or vagal nerve, and outputs nerve activity signals.

The biological activity (nerve activity) sensing means (2) are preferably installed in both the cardiac sympathetic nerve and vagal nerve in order to sense both the activities of the cardiac sympathetic nerve and vagus nerve. This is because it is known that regulation of heart rate is usually related to both cardiac sympathetic nerve and vagal nerve. Installing the sensing devices in both cardiac sympathetic nerve and vagal nerve enables heart rate to be regulated lower when the vagal activity is enhanced, and to be regulated higher when the sympathetic activity is enhanced. In other words, since heart is regulated by the two nerve systems, it is difficult to regulate heart rate to arbitrary target by only one nerve system.

Although it is preferable to provide two biological activity (nerve activity) sensing means (2) in the present invention as described above, any one of the means may be provided depending on the purpose of the system in the present invention.

The biological activity (nerve activity) sensing means (2) is exemplified by an electrode but is not limited thereto so long as it is able to sense the nerve activity and output the nerve activity signals.

The calculating means (3) receives the nerve activity signals sensed by the nerve activity sensing means (2), analyzes and processes the nerve activity signals, and calculates and outputs pacing signals for regulating heart rate.

The nerve activity signals sensed by the nerve activity sensing means (2) and the simultaneously measured heart rate are not correlated in a one-to-one manner. Therefore, it is necessary to calculate the pacing signals for regulating heart rate from the nerve activity signals by the calculating means (3).

To calculate the pacing signals for regulating heart rate from the nerve activity signals, one can use, for example, the impulse response of changes in heart rate in response to changes in nerve activity.

The pacing signals derived from the calculating means (3) are fed into the organism stimulating (pacing) means (4). The organism stimulating (pacing) means stimulates the heart based on the pacing signals to regulate heart rate.

The organism stimulating (pacing) means (4) is exemplified by a cardiac pacemaker but not limited thereto so long as it can regulate heart rate by stimulating the heart based on the pacing signals.

As described in detail above, the cardiac pacing system according to the present invention is based on the nerve activities of the cardiac sympathetic nerve and/or vagal nerve, but does not use the nerve activities themselves as the pacing signals. The system instead paces the heart based on the pacing signals with heart rate estimated from the nerve activities. Therefore, the system is excellent in specificity, sensitivity and transient response.

Next, we explain the blood pressure regulating system, the system to treat diseases described as

the second embodiment of the present invention.

The basic structure of the blood pressure regulating system according to the second embodiment is the same as the system (1) shown in Figure 2. The blood pressure regulating system according to the second embodiment comprises at least the biological activity (in this case, blood pressure) sensing means (2), the calculating means (3) and the organism (in this case, nerve) stimulating means (4).

The biological activity (blood pressure) sensing means (2) senses blood pressure, and outputs the blood pressure signal. The biological activity (blood pressure) sensing means (2) is exemplified as a pressure sensor but is not limited thereto so long as it can output the blood pressure signal by sensing blood pressure.

Baroreceptors distributed in the carotid sinus and aortic arch senses extension of arterial walls with increases in blood pressure, causes increased impulse transmission to the solitary tract nucleus of the medulla oblongata. In response to this, the solitary tract nucleus suppresses sympathetic nerve activity and stimulates parasympathetic nerve activity. On the contrary, when blood pressure is decreased, stimulation of baroreceptors decreases, the solitary tract nucleus is suppressed, parasympathetic nerve activity is suppressed, and sympathetic nerve activity is stimulated. These, in turn, increase heart rate and cause peripheral vasoconstriction and blood pressure is maintained. Veins also contract to increase venous return to the heart.

The blood pressure regulating system according to the second embodiment of this invention can be used for patients who are unable to maintain normal blood pressure due to failures in the blood pressure regulating system.

The calculating means (3) receives the blood pressure signals sensed by the biological activity (blood pressure) sensing means (2), analyzes the blood pressure signals, calculates signals to stimulate sympathetic nerve that can regulate blood pressure by stimulating the sympathetic nerve innervating vascular beds, and outputs the calculated signals to stimulate sympathetic nerve.

The blood pressure signals sensed by the biological activity (blood pressure) sensing means (2) and the sympathetic nerve activity signals are not correlated in a one-to-one manner, similarly for blood pressure regulation but not only for heart rate regulation. Therefore, it is necessary to calculate the signals to stimulate sympathetic nerve innervating vascular beds for blood pressure regulation from blood pressure signals by the calculating means (2).

To calculate the signals to stimulate sympathetic nerve innervating vascular beds for blood pressure regulation, one can use, for example, the impulse response of changes in sympathetic nerve activity in response to changes in blood pressure may be used, for example, for calculating the signals to stimulate sympathetic nerve that can regulate the blood pressure.

The organism (nerve) stimulating means (4) receives the signals to stimulate sympathetic nerve calculated by the calculating means (3), and regulates blood pressure by stimulating the sympathetic nerve innervating vascular beds based on the signals to stimulate sympathetic nerve. The sympathetic nerve stimulating sites are exemplified by sympathetic ganglia, surface of spinal cord, and preferred sites in the brain, but are not limited thereto so long as they can stimulate sympathetic nerve.

As described in detail above, the blood pressure regulating system according to the present invention is based on blood pressure, but does not use blood pressure itself as the signals to stimulate sympathetic nerve. The system instead stimulates the sympathetic nerve based on the signals to stimulate sympathetic nerve estimated from blood pressure. Therefore, the system can perform stable blood pressure regulation as native pressure regulation.

Next, we explain the cardiac disease treating system, the system to treat diseases described as the third embodiment of the present invention.

The basic structure of the cardiac disease treating system according to the third embodiment is the same as the system (1) shown in Figure 2. The cardiac disease treating system according to the third embodiment comprises at least the biological activity (in this case, cardiac activity) sensing means (2), the calculating means (3) and the organism (in this case, nerve) stimulating means (4).

The cardiac disease treating system according to the third embodiment is effective for correcting the cardiac function fallen into abnormal states by various diseases. For example, it is known that abnormal native regulation is involved in the progression of cardiac diseases, and abnormal sympathetic overactivities and vagal withdrawal have been shown with myocardial infarction. It is possible to prevent the progression of various diseases by correcting the abnormal native functional state with the system according to the present invention.

In the cardiac disease treating system according to the third embodiment, the biological activity (cardiac activity) sensing means (2) senses cardiac activity information issued by native cardiac activity and outputs cardiac activity signals. Cardiac activity information sensed by the biological activity (cardiac activity) sensing means (2) is exemplified by heart rate and electrocardiogram information.

The calculating means (3) receives cardiac activity signals sensed by the biological activity (cardiac activity) sensing means (2), analyzes and processes the cardiac activity signals, calculates signals to stimulate nerve that can regulate cardiac activities by stimulating nerves, and outputs the signals to stimulate nerve.

Before getting ill, in patients to whom the cardiac disease treating system according to the present invention may be applied, native regulatory mechanism is normally operating. Once getting ill into various cardiac diseases, however, the native regulatory mechanism does not operate towards the recovery.

In the cardiac disease treating system according to the third embodiment of the present invention, the calculating means (3) includes a discriminating means (not shown) for the discrimination whether cardiac activity information fed into the calculating means (3) arises from normal biological activities or from abnormal biological activities. By this means, the calculating means does not calculate signals to stimulate nerve stimulating signals and does not output the signals to stimulate nerve to the organism (nerve) stimulating means (4) when the heart is discriminated as normally functioning by inputting cardiac activity information sensed by the biological activity (cardiac activity) sensing means (2). In this case, the organism is regulated by its native regulatory mechanism. When the heart is discriminated as abnormally functioning by inputting cardiac activity information sensed by the biological activity (cardiac activity) sensing means (2), on the other hand, the calculating means calculates the signals to stimulate nerve so as to correct the abnormal function of the heart, and outputs the signals to the organism (nerve) stimulating means (4).

The signals to stimulate nerve derived from the calculating means (3) are fed into the organism (nerve) stimulating means (4). The organism (nerve) stimulating means (4) stimulates nerve based on the signals to stimulate nerve to regulate cardiac activities.

The organism (nerve) stimulating means (4) is exemplified by an electrode, but is not limited thereto so long as it is able to regulate cardiac activities by stimulating the nerve based on the signals to stimulate nerve. Nerve stimulating sites are exemplified by vagal nerve, aortic depressor nerve, and preferred sites in the brain, but are not limited thereto so long as they are able to regulate cardiac activities.

Test Examples

Although the present invention is explained in details with reference to the following test examples, the present invention is by no means limited to these examples.

(Test Example 1)

We ligated the anterior descending branch of left coronary artery in 20 anesthetized rats to create rats with myocardial infarction. We tabulated mortality periodically in this group.

In other 16 rats with myocardial infarction, we decreased heart rate by stimulating vagal nerve (pulse width: 2 msec, pulse voltage: 2 V, pulse frequency: 2 Hz) from 2 minutes after the onset of myocardial infarction. We also tabulated mortality periodically in this group.

In still other 15 rats with myocardial infarction, we decreased heart rate by stimulating vagal nerve (pulse width: 2 msec, pulse voltage: 2 V, pulse frequency: 5 Hz) from 2 minutes after the onset of myocardial infarction. We again tabulated mortality periodically in this group.

The results on mortality are shown in Figure 4.

The results of this Test Example have shown that all rats with myocardial infarction but with no treatment by vagal stimulation died within 30 minutes (Figure 4(a)). On the other hand, mortality after 60 minutes from the onset of the test was decreased to about 60% when the vagal nerve was stimulated with a pulse frequency of 2 Hz (Figure 4(b)). Mortality after 60 minutes was further decreased to about 20% when the vagal nerve was stimulated with a pulse frequency of 5 Hz (Figure 4(c)).

These results indicate that stimulating vagal nerve is effective in the treatment of myocardial infarction soon after its onset.

(Test Example 2)

Since the Test Example 1 was performed under anesthesia, we performed the following test to exclude the effect of anesthesia.

Blood pressure telemeter, vagal nerve tele-stimulating device and coronary artery cuff occluders to create myocardial infarction were implanted in 32 rats.

When the rats had fully recovered from surgery for one week, the descending anterior branch of left coronary artery was occluded with the use of cuff occluders in 12 rats out of 32 rats. We tabulated mortality periodically with no vagal nerve stimulation.

In other 10 rats out of 32 rats, we stimulated vagal nerve (pulse width: 0.2 msec, pulse current: 0.1 mA, pulse frequency: 20 Hz) immediately after the occlusion of coronary artery with cuff occluders for 60 minutes. We tabulated mortality periodically with vagal nerve stimulation.

In still other 10 rats out of 32 rats, we stimulated vagal nerve (pulse width: 0.2 msec, pulse current: 0.2 mA, pulse frequency: 20 Hz) immediately after the occlusion of coronary artery with cuff occluders for 60 minutes. Vagal nerve stimulation was performed with local anesthetic application proximal to the stimulation site to prevent from afferent vagal stimulation to the cerebrum (to prevent rats from being restless with the stimulation of 0.2 mA). We again tabulated mortality periodically with vagal nerve stimulation.

The results on mortality are shown in Figure 5.

As shown in Figure 5, 66% of rats died in 60 minutes after the coronary occlusion with no vagal stimulation (Figure 5 (a)). On the other hand, mortality is limited to 40% when heart rate was decreased by 20 beats per minute by vagal stimulation of 0.1 mA (Figure 5(b)). Furthermore, with vagal stimulation

of 0.2 mA, mortality is further limited to 20 % (Figure 5 (c)).

After additional observation for 2 hours, i.e. at 3 hours after the onset of the test, mortality was 83% with no vagal stimulation, 50% with vagal stimulation of 0.1 mA, and 30% with vagal stimulation of 0.2 mA, expanding the difference larger.

The above results indicate that reduction of mortality immediately after myocardial infarction is possible by correcting the abnormal regulatory function with vagal stimulation, irrespective of the presence or the absence of anesthesia.

(Test Example 3)

We performed the following tests to investigate the long-term effects.

Myocardial infarction was created under anesthesia in the same manner as in Test Example 1. Surviving rats after every attempt of resuscitation (survival rate after 1 week being ~40%) underwent another surgery 1 week after the first surgery. Blood pressure telemeter, vagal nerve tele-stimulating device and coronary artery cuff occluders to create myocardial infarction were implanted in these rats in the same manner as in Test Example 2.

After an additional 1 week, in half of the rats (13 rats), vagal stimulation was started with the stimulation condition to decrease heart rate by 20 beats (pulse width: 0.2 msec, pulse current: 0.1 to 0.13 mA, pulse frequency: 20 Hz), and the vagal nerve was stimulated for 10 seconds every 1 minute. The test was continued for 5 weeks. No vagal stimulation was applied to the remaining half of the rats (13 rats). No deaths of the rats were observed in 5 weeks.

Changes in blood pressure and heart rate were measured throughout the test period. The results are shown in Figure 6. Figure 6(a) shows the results for the rats with no vagal stimulation, and Figure 6(b) shows the results for the rats with vagal stimulation.

As show in Fig. 6, heart rate progressively decreased with vagal stimulation, but blood pressure did not change significantly with vagal stimulation.

At 5 weeks, we measured ventricular weight in these rats. The results are shown in Table 1.

Table 1

(per 1 kg of body weight)

	Biventricular weight	Left ventricular weight	Right ventricular weight
With vagal stimulation	2.71 ± 0.24 g	1.86 ± 0.12 g	0.85 ± 0.27 g
Without vagal stimulation	3.01 ± 0.31 g	2.03 ± 0.18 g	0.98 ± 0.30 g

As shown in Table 1, ventricular weight was significantly smaller in rats with vagal stimulation, indicating ventricular remodeling after myocardial infarction was suppressed. Since ventricular remodeling is known to correlate with mortality in the chronic phase of myocardial infarction, the above results indicate that vagal stimulation enables the correction of the abnormal regulatory mechanism, resulting in a decrease in long-term mortality.

(Test Example 4)

We performed the following tests to investigate the effect of vagal stimulation on the long-term mortality.

Myocardial infarction was created under anesthesia in the same manner as in Test Example 1. Surviving rats after every attempt of resuscitation (survival rate after 1 week being ~40%) underwent another surgery 1 week after the first surgery. Blood pressure telemeter, vagal nerve tele-stimulating device and coronary artery cuff occluders to create myocardial infarction were implanted in these rats in the same manner as in Test Example 2. After an additional 1 week, in half of the rats (22 rats), vagal stimulation was started with the stimulation condition to decrease heart rate by 20 beats (pulse width: 0.2 msec, pulse current: 0.1 to 0.13 mA, pulse frequency: 20 Hz), and the vagal nerve was stimulated for 10 seconds every 1 minute for 40 days. The test was continued for 180 days. No vagal stimulation was applied to the remaining half of the rats (23 rats).

As shown in Figure 7 by accumulated survival ratio during the test 8 out of 23 rats died, resulting in the final accumulated survival ratio of 0.57 (Figure 7(a)). On the other hand only 1 out of 22 rats died with vagal stimulation of 0.1 to 0.13 mA, resulting in the final accumulated survival ratio of 0.95 (Figure 7(b)).

The above results indicate that the abnormal regulatory mechanism was corrected by vagal stimulation, and long-term mortality after myocardial infarction can be reduced.

(Test Example 5)

In anesthetized Japanese white rabbits, we obtained the impulse response function of heart rate in response to cardiac sympathetic nerve activity from measured heart rate and cardiac sympathetic nerve activity. Since heart rate fluctuation is not large enough in anesthetized animals compared to in conscious animals, heart rate was artificially altered by randomly changing pressure imposed on baroreceptors.

In the concrete, 8 Japanese white rabbits were sedated and anesthetized. Pancuronium bromide and heparin sodium were intravenously injected to eliminate contaminated muscular activities and to prevent blood coagulation, respectively.

Bilateral carotid arteries, aortic depressor nerves, and vagal nerves were exposed by neck incision in rabbits. Bilateral carotid arteries were cannulated with silicone rubber tubes connected to a servo-controlled piston pump. Carotid sinus pressure was randomly changed by applying a band-limited white noise to the servo-pump. To avoid the effect of other baroreflex systems such as those arising from aortic arch baroreceptor and cardiopulmonary baroreceptor, bilateral vagal nerves and bilateral aortic depressor nerves were cut. After thoracotomy, left cardiac sympathetic nerve was separated and cut. To measure cardiac sympathetic nerve activity (SNA), a pair of platinum electrodes was attached at the proximal end. Carotid sinus pressure and the aortic pressure were also measured. Atrial electrocardiogram was measured by attaching electrodes to left atrial appendage. Atrial electrocardiogram was fed into a tachometer to measure instantaneous heart rate (HR). Measured heart rate and cardiac sympathetic nerve activity are exemplified in Figure 3(a).

Time series of cardiac sympathetic nerve activity and heart rate were divided into segments. Each segment was subjected to Fourier transform to determine power of sympathetic nerve activity ($S_{SNA-SNA}(f)$), power of heart rate ($S_{HR-HR}(f)$), and cross-power between sympathetic nerve activity and heart rate ($S_{HR-SNA}(f)$), then we calculated transfer function (H(f)) based on the following equation (Equation 1). Impulse response (h(t)) was determined by the inverse Fourier transform of the transfer function.

$$H(f) = \frac{S_{HR-SNA}(f)}{S_{SNA-SNA}(f)} \quad \ldots (1)$$

We tested how accurate we can predict heart rate from cardiac sympathetic nerve activity with the impulse response obtained by the above procedure.

Sympathetic nerve activity and heart rate were measured by the similar method as above described. We predicted heart rate from sympathetic nerve activity using a convolution integral between the above-obtained impulse response and the measured sympathetic nerve activity (Equation 2).

$$HR(t) = \sum_{\tau=1}^{N} h(\tau) \cdot SNA(t-\tau) \quad \ldots (2)$$

(where N is the length of impulse response, t is time and τ is a convolution integral parameter, and all signals were discretized at every 0.2 s.)

Correlation coefficient between measured and predicted heart rate was calculated to be as high as 0.80 to 0.96 (median: 0.88), and the error between measured and predicted heart rate was 1.4 to 6.6 beats/minutes (median: 3.1 beats/minutes), which was as small as 1.2 ± 0.7 % of the average heart rate.

From the above results, one can conclude that heart rate can be accurately predicted from cardiac sympathetic nerve activity.

(Test Example 6)

In 10 rats, we obtained the rule or the logic how the native blood pressure regulatory center (vasomotor center) determines the sympathetic nerve activity in response to blood pressure information in 10 rats. For this, we isolated baroreceptors of animals from the rest of the circulation, and measured changes in blood pressure caused by the regulatory function of vasomotor center in response to changes in pressure imposed on baroreceptors. Open-loop transfer function (H_{native}) of baroreflex system was determined from the relation between the input (pressure on baroreceptors) and output (blood pressure). Next, we measured changes in blood pressure in response to changes in sympathetic nerve stimulation. Transfer function ($H_{STM \rightarrow SAP}$) from sympathetic nerve activity (STM) to blood pressure (SAP) was determined from these data. Transfer function ($H_{BRP \rightarrow STM}$) of the vasomotor center, which characterizes the changes in sympathetic nerve activity (STM) in response to pressure on baroreceptors (BRP), was determined as $H_{native}/H_{STM \rightarrow SAP}$.

In the concrete, we anesthetized 10 rats and inserted intratracheal tubes through the mouth for artificial ventilation. Pancuronium bromide was intravenously injected to eliminate contaminating muscular activities. Arterial blood gas was monitored with blood gas measurement device. A polyethylene tube was inserted into the right femoral vein and we infused physiological saline to avoid dehydration. A catheter-tipped micromanometer was inserted into the aortic arch via the right femoral artery.

Bilateral carotid sinuses were isolated from the rest of the circulation to open the baroreflex feedback loop, and vagal nerves and aortic depressor nerves were cut. We connected carotid sinuses to a transducer and to a servo-controlled pump system with a short polyethylene tube.

Left greater splanchnic nerve was separated and was cut at the level of diaphragm. A pair of teflon-coated platinum wires was attached to the distal end. We embedded the attached ends of platinum

wires in silicone rubber. The free ends of the platinum wires were connected to a constant voltage stimulator, controlled by a computer through an D/A converter.

Carotid sinus pressure was changed at random between 100 to 120 mmHg using a servo-controlled system to determine open-loop baroreflex transfer function (H_{native}). Carotid sinus pressure and blood pressure were measured for the determination of the transfer function.

To determine the other transfer function ($H_{STM \rightarrow SAP}$), sympathetic nerve activity was changed at random between 0 to 10 Hz while carotid sinus pressure was maintained at 120 mmHg.

The transfer function ($H_{BRP \rightarrow STM}$) of vasomotor center, which characterizes the changes in sympathetic nerve activity (STM) in response to pressure on baroreceptors (BRP) was determined as $H_{native}/H_{STM \rightarrow SAP}$. Because in native animals the same pressure as blood pressure acts on baroreceptors, we programmed to calculate the required instantaneous sympathetic nerve activity (STM) to reproduce vasomotor center for given blood pressure changes (SAP) according to the following Equation (3).

$$STM(t) = \int_0^\infty h(\tau) \cdot SAP(t-\tau) d\tau \quad \ldots (3)$$

(where $h(\tau)$ is impulse response obtained by inverse Fourier transform of $H_{BRP \rightarrow STM}$)

Then, we mimicked the impaired blood pressure regulation by fixing pressure on the baroreceptors isolated from the rest of the circulation; thereby the rats were unable to detect the blood pressure change. Changes in blood pressure of the rats were measured with an artificial catheter-tipped pressure sensor.

To substitute native vasomotor centers, we predicted sympathetic nerve activity by convolution integral between blood pressure change and the impulse response of the native vasomotor center, and stimulated celiac ganglion, a sympathetic nerve ganglion, according to the predicted value.

We evaluated how the use of estimated sympathetic nerve activity for the stimulation of celiac ganglion enables the recovery from impaired blood pressure regulation by the improvement of hypotension after passive 90-degree head-up tilt tests.

For comparison, normal rats as well as rats with impaired blood pressure regulation also underwent 90-degree head-up tilt tests for the evaluation of hypotension.

The results are shown in Figure 8. Figure 8(a) shows the changes in blood pressure of the rats receiving celiac ganglion stimulation, Figure 8(b) shows the changes in blood pressure of the normal rats, and Figure 8(c) shows the changes in blood pressure of the rats with impaired blood pressure regulation.

According to the test results in 10 rats, blood pressure decreased by 34 ± 6 mmHg in 2 seconds after head-up tilt, and by 52 ± 5 mmHg in 10 seconds in the rats with impaired blood pressure regulation. On the other hand, blood pressure decreases by 21 ± 5 mmHg in 2 seconds and by 15 ± 6 mmHg in 10 seconds when artificial blood pressure regulation was applied.

As described in detail above, in the invention described in Claims 1 and 2, one can obtain biosignals based on the biological activity of the organism, and can stimulate the organism with signals to stimulate organisms, i.e., signals calculated from the biosignals as required signals to simulate the native regulation. With these, each organ can be regulated as if the central controller were normally functioning even if the central controller itself is unable to perform normal regulations by various causes. This invention can be used for various interventions such as cardiac pacing, blood pressure regulation and treatment of cardiac diseases.

In the invention described in Claim 3, since the signals to stimulate organisms are calculated with the impulse response obtained from the normal biological activity in advance, signals to stimulate organisms can be obtained as required signals to simulate the native regulation.

In the invention described in Claim 4, heart is paced according to the information from cardiac sympathetic nerve and/or vagal nerve activity, but not based on the nerve activity itself, rather based on the heart rate estimated from the nerve activity. Therefore, the system made by the present invention is excellent in specificity, sensitivity and transient response.

In the invention described in Claim 5, sympathetic nerve stimulating signals simulating native regulation are estimated from blood pressure, and the estimated sympathetic nerve stimulating signals but not blood pressure itself are used for blood pressure regulation. Therefore, stable blood pressure regulation is possible in the same manner as native regulation.

In the invention described in Claim 6, the heart is regulated by native regulatory mechanism when the activity of the heart is normal, while the heart is regulated so as to restore the normal activity when the activity of the heart is abnormal.

Potential of Industrial Use

The present invention can provide systems to treat diseases by substituting native biological regulatory function, that is capable of regulating organs as if their central controllers were normally functioning even if the central controllers themselves become abnormal by various causes; a cardiac pacing system, a blood pressure regulating system, and a cardiac disease treatment system, all of which are based on the above medical treatment system.

Abstract of the disclosure

A medical treating system based on biological activities characterized by biological activity sensing means for sensing biological activity information produced by biological activities and outputting a biological activity signal, calculating means for receiving, analyzing, and processing the biological activity signals from the biological activity sensing means, calculating an organism stimulation signal, and outputting the organism stimulation signal, and organism stimulating means for receiving the organism stimulation signal calculated by the calculating means and stimulating an organism according to the organism stimulation signal. A cardiac pacing system based on the treating system, a blood pressure regulating system, and a cardiac disease treating system are also disclosed.